Commrades in-Arms in the PCO Battle
-- Ophthalmologists in Their Youth--

Jan Worst IIIC Award Lecture
IIIC Meeting during the ASCRS
Chicago, April, 2008
Okihiro Nishi, MD

1977, Nagoya, Japan
At the Annual Congress of the SSCRS, April 25-27, 1996, Murcia
I began to perform phacoemulsification in 1979.

(Cavitron phacomachine without linear control)
“The postoperative proliferation of LECs in their many and varied manifestations enthralled me as well.
Fibrin Reaction

3 days after surgery 7 days after surgery

Nishi O. JCRS 1986
“The warmth of our friendship flows strong & deep, giving us golden memories to treasure & keep”

1982, 1987, Annual Congress of JCRS, Fukuoka

Removal and Inhibition of LECs

• Mechanical Means:
  Polishing
  Aspiration
  Ultrasound aspiration
  Cryocoagulation
  YAG laser radiation
  Osmolysis
  Dispersion aspiration
  Perfect Capsule device
Pharmaceutical Means:

- **Antimetabolites**: Daunomycin, daunorubicin, mitomycin, 5-FU, colchicine
- **Immunotoxins & cytotoxins**: Monoclonal AB against LECs + ricin, b-FGF-mitotoxin-saporin
- **Anti-cell adhesion molecule (anti-integrins)**: RGD-peptide, EDTA, Dispase
- **Other agents**: NSAID, cyclosporin A, thapsigargin, tranilast
- **Apoptosis pathway activator**: Fas-Fas ligand
- **Gene therapy**
**Capsular Fusion**

- Cataracta congenita
- Cryo-Application
- IOL onto the ant. capsule

Nishi O, Nishi K, Menapace R.
Capsule-bending ring for the prevention of PCO.
Ophthalmic Surg Lasers 1998;29:749-753
• The hydrophobic AcrySof MA60BM (1994) was found by many surgeons to be associated with less PCO.

• No space, no cells
• Capsular stretch by biconvex IOL
• Compression inhibition
• Barrier effect of the IOL
• Stickiness of the IOL surface
• Sandwich Theory
• Discontinuous capsular bend
“The hydrophobic acrylic IOL possesses 3 times greater adhesiveness than PMMA”

Sandwich Theory

Discontinuous Capaular Bend

Sharp Bend  Blunt or No Bend
Preventive Effect of an IOL with Sharp Edges on PCO

Capsular bend created by the sharp edge induces contact inhibition of migrating LECs, regardless of material composition.

The sharper the edge, the sharper the bend, the greater the preventive effect.
Ki 67

negative in the $G_0$

positive in the $G_1,S,G_2,M$
Site of the Sharp Edge

Capsular Bend

7 weeks after surgery

Anterior Capsule

Posterior Capsule

IOL

Sharp Edge

Sharp-Edged IOL
• Molecular biological approaches
  (LECs produce various cytokines, PGs and adhesion molecules)
• To determine the stem cell of LECs and target it.
IL-1ra: Interleukin-1 receptor antagonist (1994)

- M.W. : 17.25 KD
- First-described naturally occurring receptor antagonist of any cytokine
- Inhibits activity of IL-1 by binding to a specific receptor

“Only a monomaniac gets what we commonly refer to as results”

“When the solution is simple, God is answering”

-Albert Einstein-
Jan Worst IIIC Medal Lecture 2008

April 6th, 2008

ASCRS 2008, Chicago

Okihiro Nishi, MD

Nishi Eye Hospital, Osaka, Japan
Slide 1.

Thank you so much for your kind introduction. I thank also the members of the executive committee for considering me worthy of this great honor. Jan Worst's innovations have transformed the field of Ophthalmology and implant technology and to have been chosen to give the Jan Worst Lecture is a great honor for me.

Slide 2.

I met Dr. Worst 30 years ago for the first time in Nagoya in Japan, at a scientific meeting. For me, his presentation was electrifying. He demonstrated the anatomical structure of vitreous by injecting milk, into the vitreous cavity, in order to visualize its anatomy. It was striking to visualize as the white milk poured into vitreous channels, delineating the otherwise transparent and intangible vitreous structure, and in that moment, I knew for certain that I too will participate in clinical research. It is in that sense that I am humbled to receive this honor in his name.

Slide 3.

Dr. Worst compiled his findings in a book, demonstrating the vitreous body in 3-dimensions, as shown here. Here, you see bursa premacularis which has
relevance for vitreous surgery.

Slide 4.

Here is a photo taken at the dinner of the annual meeting of the Society of the Spanish Cataract Refractive Surgery that was held in Murcia. You see Dr. Worst without his glasses. I had the unique honor to clean his glasses for him at that time.

Slide 5.

I began to perform phacoemulsification in 1979 after participating in courses in Florida and California.

Slide 6.

Here is Dr. Sinskey showing me how to perform phacoemulsification.

Slide 7.

It was, however, not the superb technology alone of the phaco technique that intrigued me, but also the postoperative proliferation of LECs in their many and varied manifestations that enthralled me as well. In short, I became fascinated with PCO.
Here you see demonstrated some of these findings. Elschnig’s pearls. Fibrin reaction. Take a look at this interesting finding.

You see here the posterior capsule three days and one week after surgery, respectively. LECs have reached the posterior pole after only one week following surgery. I realized for the first time that LECs can migrate very rapidly posteriorly on to the capsule. This finding provided me with both a clue as to PCO formation as well as a strategy for the prevention of PCO. LECs must be stopped within 1-2 weeks after surgery.

In beginning to pursue the PCO issue, I, was fortunate enough to have had two mentors - Drs. Emery and Apple.

Dr. Emery was one of the leading figures in the field of PCO research at that time. Last year, in San Diego, we met again after a 10 year hiatus. It was a warm and beautiful moment for me, and hearing his beautiful English phraseolgy. again reminded me of my past admiration for his elegant manner of speaking. The warmth of our friendship flows strong and deep, permitting us golden memories to treasure and cherish.
Slide 12.

With Dr. Apple, I had the opportunity to participate in a symposium. He pointed out to me that the etiology of the complications caused in particular by residual LECs remained unsolved and needed to be addressed. Dr Apple, at that moment had provided me with the purpose and direction for my future research.

Slide 13.

After much discussion and review of the then existing PCO literatures, I published my first paper on PCO.

I was able to demonstrate that IOL implantation reduced the PCO incidence. The study suggested also that the PCO incidence might be higher when the IOL was placed out of the bag compared to in-the-bag positioning.

At that same time, Dr. Percival, a good friend of mine published similar findings.

Slide 14-15

While we recognized that in-the-bag implantation of an IOL could reduce PCO significantly, we did not have an effective surgical technique to assure in the bag positioning. That had to wait several years until the advent of the
continuous curvilinear capsulorrhexis developed by Drs. Gimbel and Neuhann.

Subsequently, many people attempted to eliminate LECs from the capsular bag to prevent PCO, and I have listed their methods here.

I, too, attempted such techniques as ultrasound aspiration, dispersion aspiration, a method that I had developed, NSAID such as indomethacin, EDTA, RGD-peptides, and IL-1 receptor antagonists.

Dr. Emery used a monoclonal antibody with a plant toxin that bound specifically to LECs, thereby destroying them. While this method did not have clinical application, I think the concept remains worthy of restudy as the antibody may enhance the effect of the drug used.

Slide 16.

There are some other unique methods. Here is Cosme Naval with Jan Worst.

Slide 17.

Dr. Naval employed a capsular fusion method for pediatric cataracts. After the nucleus and cortex were removed, cryo was applied to residual LECs beneath the anterior capsule. The IOL was implanted above the anterior capsule, effectively fusing both anterior and posterior capsules.
Slide 18.

Hara, improvising on the open PMMA ring of Nagamoto, conceived of a closed silicone capsule ring. His findings in rabbits were striking as he described, LECs accumulating around the bulky ring that did not migrate onto the posterior capsule. I will come back to this finding later.

Slide 19.

Here is Hara. We had the opportunity to visit Dr. Apple's home in Salt Lake City, Utah. You see here the young Tetz, Hansen and Kerry Solomon.

Slide 20.

Based on Hara's ring technique, Dr. Menapace and I created for clinical use a capsule bending ring with sharp edges to form a sharp bend in the posterior capsule that would prevent PCO migration posteriorly.

Slide 21.

The effect was dramatic. While the YAG laser capsulotomy rate was 8 % in the eyes with the ring, it was almost 35% in the control eyes 2 years after surgery. In this study, the hydrophilic acrylic IOL, Hydroview, known to have high rate of PCO was used.
Though the ring was very effective, its routine use in cataract surgery was problematic.

Slide 22.
Meanwhile, the hydrophobic AcrySof was found by many surgeons to be associated with significantly less PCO than was the case for other IOLs.

Slide 23.
The theories for this preventive effect of IOLs on PCO were many. Among them were the theories of no space, no cells, capsular stretch, compression, barrier effect, stickiness of the material, and the Sandwich concept.

We proposed a discontinuous capsular bend theory, otherwise referred to as capsular bending and contact inhibition. Discontinuous is a kind of mathematical concept. You cannot draw tangential lines continuously at the (discontinuous) point.

Slide 24.
Nagata and Oshika, demonstrated that the AcrySof material possessed 3 times greater adhesiveness to the lens capsule than did PMMA. This
strong adhesiveness, they theorized, accounted for the low PCO rate of AcrySof. Material.

Slide 25.

This man sitting on the summit of Mt. Matterhorn and Mt. Acconcagua, Reijo Linnola, proposed a remarkable theory.

Slide 26.

According to him, fibronectin that deposits postoperatively around the IOL and on the posterior capsule may retard the migration of LECs. Since the LECs are situated between the fibronectins on the IOL and the posterior capsule, he called this “the sandwich theory”. I think this concept may play a role in the late stage of PCO formation.

Slide 27.

Here are our research findings. With either the AcrySof or the, PMMA-IOL, each identical in design with sharp edges or with the silicone IOL with sharp edges, a sharp capsular bend was formed at the edge. When the edge was rounded by tumbling, the bending was not sharp. With the round edged IOL, there was no bending, and significant LEC migration was noted.
Slide 28.

We concluded from our research that the capsular bend created by the sharp edge of an IOL induces contact inhibition of migrating LECs, independent of the material used in the IOL. The sharper the edge, the sharper the bend, the greater the preventive effect.

Slide 29.

Our theory is based on a very common observation in cell culture. In a well with a rectangular bottom, the cells, accumulate in layers, never climb up along the well wall. Similarly, LECs cannot migrate around a sharp capsular bend.

Slide 30.

The effect of the capsular bending ring can be explained in the same way. This is a rabbit lens capsule. This corner surrounded by the anterior and posterior capsules and the capsule bending ring with sharp edges is analogous to the rectangular well bottom in the cell culture. These LECs can make layers on the ring, but they cannot migrate onto the posterior capsule.
Slide 31.

To prove our theory, we carried out Ki 67 staining of LECs. This is the well-known cell cycle. G1, S with DNA synthesis, G2 and M with mitosis. Here is G0 in which cells are at rest. They are not undergoing mitosis. According to our theory, LECs at the capsular bend should be contact-inhibited and therefore in the G0 phase. Ki67 stains cells in the G1, G2, S, and M phases, but not cells in the G0 phase.

Slide 32.

Our results. This is posterior capsule. Here is the site of capsular bending and the sharp edge of the implanted IOL. These LECs before the capsular bend are being firmly pressed resulting in the elongation of their cell nuclei. As a result, the cells here are more dense, compared to those cells beyond the capsular bend. Almost all of the cell nuclei are Ki67 negative, i.e., they are in the G0 phase of the cell cycle, thus indicating that they are contact-inhibited.

The LECs after the capsular bend show a normal appearance of their cell nuclei and are Ki67 positive, i.e., they are proliferating, as you can recognize in the brown stained nuclei.

Because there is no continuation of cells at the capsular bend site, those
LEC\text{s must have migrated and proliferated prior to the formation of the capsular bend. We concluded, therefore, that the capsular bending must be formed before LECs migrate posteriorly, to prevent PCO formation. Up to 3-4 weeks after surgery is the crucial and critical period for the prevention of PCO.

Slide 33.

What about the LECs in the equatorial region?

Here is the bend site. These LECs are contact-inhibited, as we have just seen in the previous slide. The LECs here in the equatorial region have undergone lens fiber cell change and have formed a Soemmering’s ring.

Slide 34.

This pattern can be always observed in those eye that received a sharp edged IOL. This histopathological picture which I cite from the paper of Drs .Mamalis and Liliana, shows, in my opinion, a similar finding. Here, the LECs before the capsular bend ought to be contact-inhibited. These cells in the equatorial region have undergone lens fiber cell change, forming a Soemmering’s ring.
Slide 35.

Many clinical studies showing the inhibitory effect of sharp edged IOLs on PCO formation have employed such evaluation methods as POCO, EPCO, AQUA, and others. We have to be grateful to those who developed such tools to verify the presence of PCO.

Slide 36.

Drs Spalton, Menapace, Tetz and Auffarth. They have all contributed tremendously to clinical PCO research.

Slide 37.

To date, there exists, with the exception of some devices of limited usefulness, but one effective clinical tool to retard PCO formation, namely, the sharp-edged IOL.

Molecular biological approaches, including the determination of the actual stem cell precursor of the LEC, hold the promise for future safe clinical approaches to eliminate PCO. Similar to researchers searching for cancer stem cells for selective destruction, so should we be searching to single out and eliminate stem cells responsible for LEC.
As one example, I want to demonstrate the effect of a molecular biological approach which was the most effective method that I experienced in my research. IL-1 receptor antagonist is the first-described naturally occurring receptor antagonist of any cytokine. It inhibits activity of IL-1 by binding to a specific receptor. LECs produce various cytokines including IL-1.

IL-1 was injected into the anterior chamber at the end of surgery. Just one shot. Here, you see the absence of LECs on the posterior capsule compared to the control.

IL-1 has reduced the inflammatory response as well.

Similar to this anti-cytokine therapy in concept is the current anti-VEGF therapy targeting the abnormal aneogenesis underlying various retinal vascular diseases.

Clearly, we must continue our effort to pursue such methods in the future for the prevention of PCO keeping in mind the long arduous work this entails.

As Einstein stated, “Only a monomaniac gets what we commonly refer to as
results”.

“When the solution is simple, God is answering”

From the clinical view, developing such a simple method must be our goal.

Slide 41.

Last, but not least, I want to thank my many friends for their support and friendship.

Camille Budo, John Alpar, Aziz Anis, the late Michael Blumenthal, Sam Masket, Howard Fine, Emanuel Rosen, Philippe Sourdille, Doug Koch, Albert Galand, Patrick Condon, Terrence O’Brien, Chandrappa Reshmi, Thomas Neuhann, Richard Packard, Robert Drews, Ehud Assia, Leif Corydon, Jack Dodick, Harry Brabow and naturally my Japanese colleagues and many others whom I may have failed, inadvertently, to mention. I remember often Dr. Drews and his kindness. More than twenty years ago at the ASCRS in Los Angeles, I presented the anterior capsule suturing technique using 10-0 nylon. Next year during the ASCRS, Dr. Drews came to me and handed a package of 11-0 nylon that was not available in Japan. I was moved by his kindness and big, generous American mind.

I am both blessed to have many such good friends. Such friendships, to a great degree, provide the support and encouragement for me to continue to
pursue clinical research.

Again, I thank all of you for the honor of delivering the Jan Worst Lecture.